REMARKS

Claims 1-50 are pending. Claims 9-11, 29, and 30 stand withdrawn from consideration as being drawn to nonelected subject matter. Applicants have added new claims 51 and 52, both of which find support in the Specification, e.g., at page 4, lines 6-8. Claims 1-8, 12-28, and 31-52 will therefore be pending upon entry of the proposed amendments.

Claims 1-8, 12-28, and 31-50 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Crumb et al., U.S. Patent No. 6,030,943 (Crumb) in view of Brown et al., U.S. Patent 5,573,781 (Brown). According to the Office (Office Action, pages 3-4, emphasis added):

> Furthermore, Brown beneficially teaches that the claimed co-solvent of alkanol (i.e. ethanol etc) is an effective delivery carrier and/or effective delivery enhancer/vehicle to aid in the injectable administration of an active ingredient to a subject (see e.g. entire document including column 7 lines 9-26, tables and claims).
>
> It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify Crumb et al.'s pharmaceutical composition and/or kit to include Brown's alkanol active ingredient within Crumb's pharmaceutical composition and/or kit because the two combined teachings would create the claimed pharmaceutical composition and/or kit for enhanced injectable delivery of the pharmaceutical composition's active ingredients to a subject.

This is respectfully traversed.

Brief Summary of Claimed Subject Matter

The present claims are directed to kits and pharmaceutical compositions for the parenteral administration of didemnin compounds (e.g., aplidine, which is also known as dehydrodidemnin B).

Independent claim 1 is directed to kits that include "firstly a lyophilized didemnin preparation comprising water-soluble material and secondly, and separately contained, a

reconstitution solution of mixed solvents, wherein the reconstitution solution of mixed solvents comprises water for injection and a co-solvent."

Independent claim 12 is directed to reconstituted pharmaceutical compositions that include: "a didemnin compound; a water soluble material; a surfactant; an alkanol; and water for injection."

Independent claim 33 is directed to kits that include "firstly a lyophilized didemnin preparation comprising water-soluble material and secondly, and separately contained, a reconstitution solution of mixed solvents, wherein the reconstitution solution of mixed solvents comprises water and a co-solvent, wherein:

(i) the water is present in an amount sufficient to allow solubilization of the water soluble material, and

(ii) the co-solvent is present in an amount sufficient to allow solubilization of the didemnin in the lyophilized didemnin preparation."

Independent claim 41 is directed to reconstituted pharmaceutical compositions that include:

"a didemnin compound;

a water soluble material;

a surfactant;

an alkanol, wherein the alkanol is present in an amount sufficient to allow solubilization of the didemnin compound; and

water, wherein the water is present in an amount sufficient to allow solubilization of the water soluble material."

The claimed kits and pharmaceutical compositions address some of the problems associated with prior efforts to obtain stable, soluble pharmaceutical preparations that are suitable for the parenteral (e.g., intravenous) administration of didemnins. Stable didemnin pharmaceutical preparations can typically be achieved by the inclusion of a bulking agent as part of the preparation. A preferred bulking agent for this purpose is mannitol, which is water

soluble. The didemnins (e.g., aplidine), however, tend to have only rather limited water solubility. This difference in water solubility makes the solubilization of a didemnin (e.g., aplidine) and a water soluble adjuvant(s) (e.g., mannitol) in water based vehicles difficult. Water based vehicles, such as normal saline 0.9% NaCl, are typically the liquid vehicles of choice for intravascular routes of administration.

The inventors, in addressing the aforementioned problems, have discovered lyophilized didemnin preparations, which are both stable and permit solubilization of a didemnin (e.g., aplidine) and a water soluble adjuvant(s) (e.g., mannitol) in water based vehicles that are suitable for parenteral (eg.intravascular) administration to a cancer patient.

Crumb

Crumb discloses that aplidine can be used as an L-type calcium channel enhancer (Crumb, col. 2, lines 33-34). Crumb teaches that aplidine can be administered "intravenously or by injection" using "liquids" that contain a **single** solvent, namely **water** (see Crumb at col. 6, lines 12-18). A co-solvent (e.g., an alkanol) is never mentioned in Crumb.

Brown

[1] Brown is concerned generally with methods and compositions for treating a cellular proliferative disease. A didemnin is never mentioned in Brown.

As will be discussed in more detail below, Brown teaches "substantially anhydrous" compositions (see, e.g., Brown's abstract and col.2, line 23), which include a "water immiscible" component (see, e.g., Brown's abstract and col.2, line 23); and that such compositions can be used to deliver agents that are insoluble or sparingly soluble in water.

[2] In the background section of the patent, Brown states that "some chemotherapeutic agents are poorly water soluble" (Brown, col. 1, lines 35-36). Brown then goes on to discuss a potential drawback associated with using an aqueous vehicle to intravenously administer such agents (Brown, col. 1, lines 35-41):

> Furthermore, some chemotherapeutic agents are poorly water soluble. Thus, to be administered intravenously (one particular mode of systemic administration) they must be diluted in large volumes of an aqueous vehicle. However, dilution of the drug in this manner can limit the dosage level of the drug that can be achieved in the host blood stream or in proliferative disease tissue.

[3] Brown instead of dealing with the poor water solubility of said chemotherapeutic agents, has taken a completely different approach. Brown is not concerned with trying to increase the solubility of said chemotherapeutic agents in water based vehicles for intravascular injection, but with providing an improved delivery vehicle for regional administration. In particular, Brown introduces his methods and "substantially anhydrous", injectable semi-solid compositions, which act as a depot for a cytostatic agent and are administered intralesionally:

> Methods and compositions are provided for the treatment of a host with a cellular proliferative disease, particularly a neoplasia. In the subject methods, pharmaceutically acceptable, **substantially anhydrous**, injectable, semi-solid compositions which act as depots for a cytostatic agent, are administered at the site of a lesion of the disease, particularly intralesionally. The subject compositions comprise a **water immiscible**, fatty acid ester matrix and a cytostatic agent (Brown, see Abstract and col. 2, lines 20-27, emphases added).

Thus, in Brown a different administration route is used: the cytostatic agent is administered locally, via intralesional injection. Therefore, the solubility requirements in Brown are different from the requirements of the claimed invention wherein an intravascular route of administration is used and therefore the pharmaceutical composition should be soluble in a water-based delivery vehicle. Further, in Brown a different pharmaceutical form is used: an injectable, substantially anhydrous semi-solid composition which acts as a depot (which allows the slow release of the cytostatic agent).

[4] Applicants now turn to the role of alkanols in the Brown compositions.

In the claimed kits and compositions, an alkanol is used as a co-solvent in an aqueous reconstitution solution (preferably, water 50-80% v/v) to dissolve a didemnin preparation and further be used in a water based delivery vehicle, for example diluted with normal saline, for intravascular administration.

Brown is not concerned with the solubility of cytostatic agents in an aqueous delivery vehicle.

In Brown, it is mentioned that an alkanol, preferably a lower alkanol of from 2 to 3 carbon atoms, can "optionally" be included in the carrier composition (see col.3 lines 31-41). In addition to being "substantially anhydrous," the Brown compositions also include a "water immiscible" material as a base component. More specifically, this component is a lipid matrix (see Brown at col. 2, lines 43-44: "[t]he first component of the subject carrier compositions is a water immiscible lipid matrix"). In other words, one of the required components of the Brown compositions is a material (i.e., a lipid matrix), which from a solubility standpoint, is incompatible with water. In addition, Brown explicitly tells one **not** to use lipid matrix materials, which are modified with functional groups that impart water solubility to the lipid matrix (Brown at col. 3, lines 16-21, emphasis added):

> The fatty acid esters of the subject invention **will not include** esters which are modified with additional functional groups which increase the water solubility properties of the esters, e.g. such as polyoxyethylated castor oil or other alkyleneoxy modified fatty acid esters.

Thus, Brown describes the "optional" use of an alkanol, as a solvent or a diluent for a cytostatic agent, but said solution is subsequently combined with a fatty acid ester matrix, a hydrophobic delivery vehicle.

As mentioned above, the Brown compositions are "substantially anhydrous," meaning that the compositions include little or effectively no water. See Brown at col. 6, lines 61-65:

> The subject compositions are also substantially anhydrous, whereby substantially anhydrous is meant that the delivery vehicles are not more than about 5 weight %, preferably less than about 1 weight %, and more preferably less than about 0.2 weight % water.

Clearly, Brown appears to view water as more of an impurity in, rather than an ingredient of, his substantially anhydrous compositions. This is in stark contrast to the present claims, which require the presence of a specific grade of water (i.e., water for injection) or the presence of a specific amount of water (i.e., an amount sufficient to allow solubilization of the water soluble material).

Further, Brown touts his substantially anhydrous compositions as being "particularly suited" for delivering agents that are, e.g., insoluble or sparingly soluble in water (Brown, col. 4, lines 53-57):

> The anhydrous nature of the subject compositions makes the compositions particularly suited for the delivery of insoluble or sparingly soluble agents, as well as agents that contain functional groups which may adversely interact with the components of an aqueous delivery vehicle.

Clearly, the intended use of a lower alkanol in Brown is not to increase the solubility of a cytotoxic agent in an aqueous delivery vehicle.

[5] Applicants submit that the present claims are not obvious over Crumb and Brown (alone or in combination) because to combine these two references in the manner proposed by the Office would require that a person of ordinary skill in the art ignore the teaching away in Brown to make this particular combination. This is discussed in more detail below.

Crumb teaches that aplidine, which is poorly soluble in water, can be administered "intravenously or by injection" using "liquids" that contain a **single** solvent, namely **water** (see Crumb at col. 6, lines 12-18). A co-solvent (e.g., an alkanol) is never mentioned in Crumb.

In contrast, Brown discloses compositions that are "substantially anhydrous," i.e., compositions that include little or effectively no water. Brown teaches that his substantially anhydrous compositions are "particularly suited" for delivering cytostatic agents that are

insoluble or sparingly soluble in water. One of the required components of the Brown compositions is a water immiscible lipid matrix, which from a solubility standpoint, would be incompatible with water (similar guidance is provided with respect to alkanols at col. 7, lines 9-26 of Brown). In addition, Brown explicitly tells one **not** to use lipid matrix materials modified with functional groups that impart water solubility to the matrix.

In short, Brown teaches away from the use of water-containing compositions. As such, a person of ordinary skill in the art would not have been led to combine Crumb, which is about administering a poorly water soluble drug (aplidine) in water, with Brown, which tells one to administer poorly water soluble cytostatic agents in anhydrous compositions (compositions that exclude water) that contain materials, which from a solubility standpoint, would be incompatible with water. In view of the foregoing, Applicants respectfully request that the rejection be reconsidered and withdrawn.

CONCLUSION

Applicants hereby respectfully request a telephone interview if, in the Examiner's view, the foregoing amendments and remarks do place the present application in condition for allowance.

The fee of $120 for the One Month Petition for Extension of Time to and including November 11, 2007. Please apply all charges or credits to deposit account 06-1050, referencing Attorney Docket No.: 14620-012US1.

Respectfully submitted,

Date: October 30, 2007

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